Electronic Data Submission and Utilization in Japan

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Outline

• Current situation of e-data submission
• Preparation for the end of the transitional period
• Utilization of accumulated data
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• Current situation of e-data submission
• Preparation for the end of the transitional period
• Utilization of accumulated data
Accumulation and utilization of data

NDA submission
- e-Submission of data
  - Submission of electronic data from clinical and nonclinical studies
- Storage of electronic data in the dedicated server and registration in the database
- Visualization and analysis of data, supported by browsing software

Regulatory Review
- Use of electronic data
  - Accessible, visualized electronic data for each reviewer
  - Easy to identify individual clinical case data, drilling down of data
  - Operation of various analyses - simple, subgroup analysis for the present

Utilization of Accumulated Data
- Integration of cross-products information
  - Utilization of exhaustive information by therapeutic category for review/consultation
  - Internal review on particular theme – e.g.) active utilization of M&S
    - Review on pediatric dosage
    - Preparation of disease model
    - Development of evaluation indicator
  - Utilization in preparation of guideline

What the review authority can do with the information of all products.

Submission of electronic clinical study data has started since Oct 1st 2016!

Scientific discussion and decision making on the basis of internal analysis result

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab
## Timeline for implementation of e-data submission

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### Key Events:
- **2018/05/01** - PharmaSUG 2018
- **Today** - Today
- **Mar 31** - End of the transitional period
- **Oct 1** - Initiation of e-study data submission
- **3.5 years of Transitional period**
- **PMDA Validation Rules**
- **Issuance of “Basic Principles”**
- **Issuance of “Technical Conformance Guide”**
- **Issuance of “Notification on Practical Operations”**
- **FAQ**
- **Data Standards Catalog**
- **PMDA Validation Rules**
- **Briefing/Workshop**
- **Portal Site Open**
- **Today**
- **Preparation for the end of transitional period (Revision of the notifications, etc)**

### Regular Update
- **Regular Update**
Notifications, Guide, FAQs, and Standards Catalog

- **Basic Principles** on Electronic Submission of Study Data for New Drug Applications (Jun 20, 2014) and Q&A
  - The first official announcement that MHLW/PMDA will require CDISC-standardized study data for NDA.
- **Notification on Practical Operations** of Electronic Study Data Submissions (Apr 27, 2015) and Q&A
  - Practical issues on e-Study data submission
- **Technical Conformance Guide** on Electronic Study Data Submissions (Latest update on Sep 11, 2017)
  - Technical details on e-Study data submission
- **FAQ website** (Latest update on Mar 7, 2018)
  - Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and the guide
- **PMDA Data Standards Catalog** (Latest update on Mar 3, 2017)
  - List of acceptable versions of Data Exchange Standards and Terminology Standards
CDISC validation in PMDA

- PMDA validation rules were published on Nov 18, 2015
- We use Pinnacle 21 Enterprise for CDISC validation
  - Apply to SDTM, ADaM, CT, and Define-XML
  - PMDA validation rules are provided on the PMDA website for sponsor’s use.
  - Sponsors should use the same validation rules and check the results in advance.
- Three levels of severity of the errors
  - **Reject** (a) Rules which, if violated, will cause the review to be suspended until corrections have been made
  - **Error** (b) Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made
  - **Warning** (c) Rules which, even when violated, will not necessarily require any explanation
Consultation for clinical e-data submission

- 140 consultation meetings have been requested by 44 companies as of March 31, 2018.

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<th>Year</th>
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<td>J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)</td>
<td>65</td>
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<td>Total</td>
<td>140</td>
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- Multiple meetings have been held for some products.
- Various characteristics
  - With/without official minutes
  - Japanese/foreign company
  - Oncology and other therapeutic areas
  - Time of consultation meeting during drug development
Frequently raised issues at consultation meetings

• Majority of issues is explanation of validation results at this point
  – Sponsor’s validation results and reasons of “Error”

• Other issues
  – Product dependent issues such as use of SUPPQUAL, custom domains, and traceability
  – Information to be included in the Trial Design Model
  – Issues related to WHO DDs coding
  – SI units
  – How to submit study data for multiple time points
  – Use of particular variables such as USUBJID, RACE
  – Submission format for clinical pharmacology data

• Corrections of consultation materials
  – Ex. Application form, SDRG, ADRG...
Data submitted with new drug applications

• 41 NDAs were submitted with electronic study data by 26 companies as of Mar 31, 2018.
  – Although several issues below have occurred during data transmission, all the submitted data are successfully received.
    • System issues
    • Validation failure because of violations categorized “Reject”.
    • Lack of explanations for “Error” issues.
  – Various characteristics on the NDAs
    • Domestic/global company
    • Oncology holds majority, but submissions in other areas are also increasing
    • Initial application / application for partial changes (supplemental application)
    • Clinical pharmacology study
PMDA requests applicants to submit various information for explanation on study data, and they are very useful for reviewers.

- Analysis Results Metadata
- Reviewer’s Guide (SDRG, ADRG)
- Define.xml
- Programs for creating ADaM datasets

Analysis Results Metadata will be the key in their review with electronic data.

- Most reviewers usually start with confirming the reproducibility of the primary results in CTDs, and Analysis Results Metadata is very useful for reviewers for their quick access to the analysis datasets used.

So far, we have not received major questions/concerns about the submitted data or data format during new drug review period.

We strongly recommend that you include “Creating ARM” in your plan of organizing submission datasets.
Other topics of e-data submission

• CDISC Validation in PMDA
  – We plan to update our CDISC validation software and PMDA validation rules in the near future.
  – We are considering smooth transition to the new version and the detailed information will be provided in advance.

• Use of non-clinical data (SEND)
  – We continue to discuss how we can efficiently use non-clinical study data in our review process.
  – Submission timing will be one of the topics in the discussion.

• Therapeutic Area Standards
  – We continue to work for incorporating medical practices in Japan to Therapeutic Area User Guides in collaboration with academic societies and industry, mainly in the Public Review period.
  – We basically accept that applicants implement the published TAUGs.
Outline

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• Preparation for the end of the transitional period
• Utilization of accumulated data
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Today: 2018/05/01

PharmaSUG 2018

14
The transitional period will be ended on March 31, 2020.

- During the transitional period, applicants can submit the data of at least one clinical trial included in their clinical data packages.
- After the period, applicants need to submit the data of all the requested clinical trials.

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If submission date is after this date, applicants need to submit the data of all the requested clinical trials.
Preparation for the end of transitional period

We are considering revision of notifications and clarification, for example,

- Revision of notifications with considering situation when applicants can not use Electronic Submission Gateway
- Clarification of relationship between
  - Electronic study data submission
  - Submission of eCTD
  - Use of Electronic Submission Gateway
- Clarification of timing of data submission for special situation
  - Ex. New drug applications for anti-HIV drugs

We will proceed the project with continual discussion with industry for the smooth transition to the next phase.
Outline

• Current situation of e-data submission
• Preparation for the end of the transitional period
• Utilization of accumulated data
## Process of starting to analyze data

### At any time during the development, multiple times

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<th>Data Submission</th>
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**Clinical trial consultations**
- Discussion about which study should be included in e-study data submission

**Consultation for electronic study data submission**
- Discussion about technical issues of e-study data submission

**Pre-application meeting on procedures for new drug review**
- Confirmation of the e-study data submission and the schedule of the NDA
  - Finalized the form for consultation (Exhibit 8)

**Validation**
- Check the result based on “Exhibit 8”

**Confirmation of submitted data sufficiency**
- Check whether submitted data are sufficient based on “Exhibit 8”

**Start to analyze data**
## Review process and data analysis

### Review Process
- **Before the First Team Meeting**
  - Confirmation of reproducibility of the primary analysis
  - Analyses for review points
    - Indication, dosage, etc
    - Consistency, AE, individual patient profile, etc
  - Analysis for exploring review points
    - Factors affecting efficacy and safety
- **After Expert Discussion**
  - Additional analysis taking comments from external experts into account
    - Indication, dosage, special population

### Analysis Timing

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<td>After the First Team Meeting</td>
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<td><strong>Analyses related to inquiries</strong></td>
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<td>- Consider contents of inquiries based on results of analyses</td>
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<tr>
<td>- Consider necessity for additional inquiries after receiving answers</td>
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### Completion of Review
- **First Team meeting**
- **Meeting with Sponsor**
- **Inquiries/Answers**
- **Discussion with Experts**
- **Inquiries/Answers**
- **After Expert Discussion**
- **Inquiries/Answers**
Analyses of CDISC data in review team

Common analyses to many clinical trials
- Distribution of patient demographics
- Changes in laboratory data
- Adverse events rates

Software: JMP, Clinical, etc.
Datasets: SDTM

General analyses for efficacy and safety data
- Simple analyses depending on the characteristics of evaluation variables – continuous/categorical/time-to-event)

Software: JMP, SAS etc.
Datasets: ADaM

Relatively complicated analyses
- Analyses with programming (innovative/complicated analyses)
- Simulations

Software: SAS, etc.
Datasets: SDTM, ADaM
Regulatory Science Center established on Apr 1
PMDA initiatives for quantitative science

• Several initiatives/activities for quantitative science are established and are in execution for new drug/device development and review in Japan.
• We are considering how we can efficiently use those data that we will obtain in each stage of clinical development.

Use of data standards is the key for all the initiatives
As the first step of GCP Renovation, the Expert Working Group has started the discussion of revision of E8 Guidance.

ICH: The International Council for Harmonisation
ICH E8: General considerations for clinical trials
ICH E6: Good Clinical Practice

Reflection Paper of GCP Renovation

Utilization of study data in the future

Utilization of study data for new drug review
- Improvement of predictability of efficacy and safety
- Reviewing M&S results
- Reviewing novel evaluation methods
- Swift and effective decision-making

Utilization of accumulated study data
- Data accumulation
- Experiences of data evaluation
- Consultation based on the cross-product information
- Guidance for therapeutic areas
- Issuance of points to consider for methodology

Efficient new drug development
- Use of consultation meeting based on the cross-product information by PMDA
- Active use of M&S
- Use of innovative and appropriate methods for the purpose

Use of various data sources in the future
- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources

Submission of standardized study data
- Consultation/guidance about innovative analysis methods
- Contribution to data standardization
Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - All data has been successfully received since Oct 1, 2016.
- PMDA will continue to provide information on the e-data submission for industries with considering the end of transitional period.
  - The transitional period will be ended on Mar 31, 2020.
- Utilization of various data sources will be on the table of international discussion. Data standards will be the key for the activities and further cooperation with industry, CDISC, and other regulatory agencies will be more important.
- We appreciate continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug.